Coronary endothelial function testing provides superior discrimination compared with standard clinical risk scoring in prediction of cardiovascular events

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Abstract: BACKGROUND Endothelial dysfunction is regarded as the early stage of atherosclerosis and is associated with cardiovascular (CV) events. This study was designed to determine whether assessment of coronary endothelial function (CEF) is safe and can reclassify risk in patients with early coronary artery disease beyond the Framingham risk score (FRS). METHODS AND RESULTS CEF was evaluated using intracoronary acetylcholine in 470 patients who presented with chest pain and nonobstructive coronary artery disease. CV events were assessed after a median follow-up of 9.7 years. The association between CEF and CV events was examined, and the net reclassification improvement index (NRI) was used to compare the incremental contribution of CEF when added to FRS.The mean age was 53 years, and 68% of the patients were women with a median FRS of 8. Complications (coronary dissection) occurred in three (0.6%) and CV events in 61 (13%) patients. In univariate analysis, microvascular CEF [hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.72-0.97, P=0.032] and epicardial CEF (HR 0.73, 95% CI 0.59-0.90, P=0.01) were found to be significant predictors of CV events, whereas FRS was not (HR 1.05, 95% CI 0.85-1.26, P=0.61). When added to FRS, microvascular CEF correctly reclassified 11.3% of patients [NRI 0.11 (95% CI 0.019-0.21)], epicardial CEF correctly reclassified 12.1% of patients [NRI 0.12 (95% CI -0.02 to 0.26)], and the combined microvascular and epicardial CEF correctly reclassified 22.8% of patients [NRI 0.23 (95% CI 0.08-0.37)]. CONCLUSION CEF testing is safe and adds value to the FRS, with superior discrimination and risk stratification compared with FRS alone in patients presenting with chest pain or suspected ischemia.

DOI: https://doi.org/10.1097/MCA.0000000000000347

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Coronary Artery Disease 2016, **27:**213–220

Keywords: cardiovascular events, endothelial dysfunction, endothelium, myocardial infarction, prognosis

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Received 12 November 2015 **Revised** 8 December 2015
Accepted 23 December 2015

Introduction

Globally, cardiovascular (CV) diseases are the number one cause of death and a leading cause of morbidity [1]. Traditional CV risk factors based on the Framingham study have been used to estimate an individual global CV risk [2]. Practice guidelines use the Framingham risk score (FRS) to classify individuals as low, intermediate, or high risk and to determine their target cholesterol levels for primary prevention [3].

However, these traditional risk factors as identified in the Framingham study have been inconsistent in predicting CV events when applied to different populations and correctly assigned the risk of the development of coronary heart disease only in half of the cases [4]. This underscores the complex interplay between traditional CV risk factors, genetic predisposition, and other atheroprotective factors prevalent in individuals of different populations in predicting CV events.

Functional vascular abnormalities such as endothelial dysfunction are considered a key event in the initiation, progression, and complications of coronary artery disease. Endothelial dysfunction is a systemic disorder affecting multiple vascular beds and can be considered as the integrated index of both the overall CV risk factor burden and the sum of genetic risk factors and environmental factors [4].

Previous studies have shown an association between the presence of both coronary and systemic endothelial dysfunction and an increased risk for future CV events [5–8]. We have previously summarized the role of endothelial function testing in predicting CV events [9]. No published studies, however, have evaluated how measures of coronary endothelial function (CEF) affect discrimination of the FRS.

Invasive measurement of the change in coronary blood flow (CBF) in response to an intracoronary infusion of acetylcholine (ACh) is considered the reference standard in CEF testing [10]. However, the invasive nature and potential safety concerns of this method limit its use [10]. To our knowledge, no previous study has compared the

DOI: 10.1097/MCA.0000000000000347

efficacy of the FRS with that of invasive CEF in predicting CV events. This study was designed to test the hypothesis that coronary epicardial and microvascular endothelial function testing is safe and improves the predictive accuracy and classification of the FRS in patients with nonobstructive coronary artery disease.

Methods

Study design

This study is a prospective single-center cohort study. The study was approved by the Mayo Clinic Institutional Review Board, and informed consent was obtained from all patients.

Study population

The study group consisted of 470 patients with chest pain who were referred to the cardiac catheterization laboratory for evaluation of coronary artery disease, were found to have nonobstructive disease, and underwent a comprehensive coronary physiology study, including assessment of endothelial dependent and independent functions.

Exclusion criteria included the following: significant coronary artery stenosis ($>40\%$), ejection fraction less than 45%, unstable angina, previous acute coronary syndrome, significant systemic disease, and pregnancy. Medications that may affect CV hemodynamics were discontinued for at least 48 h before the study.

Study protocol

At baseline, diagnostic coronary angiography and determination of endothelium-dependent changes in CBF and endothelium-independent coronary flow reserve were performed as described previously [11–14]. A Doppler guidewire (0.014 inches in diameter; FloWire; Volcano Incorporated, San Diego, California, USA) within a 2.2 F coronary infusion catheter (Ultrafuse; SciMed Life Systems, Maple Grove, Minnesota, USA) was advanced and positioned in the middle portion of the left anterior descending coronary artery (LAD). Intracoronary bolus injections of incremental doses (18–72 μg) of adenosine (Fujisawa, Kanagawa, Japan), an endothelium-independent vasodilator (primarily of the microcirculation) [15], were administered into the guiding catheter until maximal hyperemia was achieved.

Assessment of endothelium-dependent changes in vascular diameter and CBF was performed by selective infusion of ACh into the LAD. ACh (10^{-6}, 10^{-5}, and 10^{-4} mol/l; Iolab Pharmaceuticals, Rancho Cucamonga, California, USA) was infused at a rate of 1 ml/min for 3 min [12,16]. Hemodynamic data (heart rate and mean arterial pressure), Doppler measurements, and coronary angiography data were obtained after each infusion. Endothelium-independent epicardial vasodilation was assessed with an intracoronary bolus injection of nitroglycerin (200 μg; Abbott Laboratories, Abbott Park, Illinois, USA) [17].

Epicardial coronary endothelial function

The coronary artery diameter was analyzed by quantitative coronary angiograms from digital images using a modification of a previously described technique from this institution [11,12]. The LAD was divided into proximal, middle, and distal segments. For each segment, measurements were performed in the region in which the greatest change had occurred during ACh infusion. An angiographically smooth segment of the proximal, middle, and distal LAD, free from any overlapping branch vessels, was identified in each patient and served as the reference diameter for the calculation of the diameter of stenosis. End-diastolic cine frames that best showed the segment were selected, and calibration of the video and cine images was done, identifying the diameter of the guide catheter. Quantitative measurements of the coronary arteries were obtained using a computer-based image analysis system. Segment diameters were determined at baseline and after both ACh and nitroglycerin administration. The proximal segment was not exposed to ACh and thus served as a control segment.

Microvascular coronary endothelial function

Doppler flow velocity spectra were analyzed online to determine the time-averaged peak velocity. Volumetric CBF was determined from the following relation: $\text{CBF} = \text{cross-sectional area} \times \text{average peak velocity} \times 0.5$ [18]. Endothelium-dependent microvascular function was calculated as % ΔCBF in response to ACh as previously described [19].

Follow-up

Long-term follow-up was performed through a detailed questionnaire inquiring about occurrence and dates and timings of CV events. The vital status of the patients was determined using the National Death Index. For patients experiencing more than one CV event, only the first event was considered in the analysis. All CV events were confirmed by a review of the hospital records.

A composite endpoint of CV death, acute myocardial infarction, stroke, coronary artery bypass graft surgery, repeat coronary angiography, and percutaneous coronary intervention and other vascular surgeries (endarterectomy, repair of an abdominal aortic aneurysm, or peripheral bypass surgeries) was assessed during the follow-up.

Statistical analysis

Data are expressed as mean ± SD or count and percentage, as appropriate. Variables with heavily skewed distribution are reported as medians with first and third quartiles in parentheses. The statistical analysis was carried out by an independent statistician.

Survival analysis

The starting point for all survival analysis was the date of the CEF angiogram. The composite of CV events was the primary endpoint, and the patient's survival time was the interval from the date of the endothelial function angiogram to the date of the first event. For patients who did not have an event, the event-free survival time was the interval from the endothelial function angiogram to December 2010.

The FRS was then calculated for each patient using the original variables of the 10-year FRS (age, sex, cigarette smoking status, blood pressure, antihypertensive medication use, total cholesterol level, high-density lipoprotein level, and the presence of diabetes mellitus) [2]. The FRS score was then refitted using a multivariable Cox proportional-hazards model. This baseline model was then extended to three other models by including microvascular CEF (% ΔCBF), then epicardial CEF (% ΔCAD), and finally both microvascular and epicardial CEF. For each of the models, the 10-year absolute risk of developing CV events was calculated and used to classify patients as low (< 10%), intermediate (10–20%), and high (>20%) risk on the basis of the Adult Treatment Panel III classification [3].

The Cox proportional-hazards multivariable regression analysis was used to determine the univariate and multivariable relationships between the FRS, microvascular CEF, epicardial CEF, and CV events during the follow-up period. All probability values were two-tailed, and a *P*-value of 0.05 was considered statistically significant.

Net reclassification improvement index

The net reclassification improvement index (NRI) was calculated to assess whether microvascular CEF, epicardial CEF, or combined microvascular and epicardial CEF improved discrimination of the FRS using methods developed by Pencina *et al.* [20]. The NRI calculates the percentage of correct movement across categories for those with and those without events. The NRI assesses the probability of being correctly reclassified to a higher risk category for patients with events minus the probability of being incorrectly reclassified to a lower risk category for patients with events plus the probability of being correctly reclassified to a lower risk category for patients with no events minus the probability of being incorrectly classified to a higher risk category for patients with no events. As the risk prediction models were based on time-to-event data, the NRI was calculated using methods that took survival time into account [21,22]. The corresponding 95% confidence intervals (CIs) were obtained with bootstrapping.

Results

Study cohort

We studied 470 patients with a mean ± SD age of 53 ± 12 years, 68% of whom were women. The median (IQR) FRS was 8 (4.2–15.2).

The % ΔCBF (mean ± SD) was 61.5 ± 164.6 and the % ΔCAD was − 15.2 ± 24.8. The baseline characteristics of the cohort at the time of coronary vascular testing are shown in Tables 1 and 2.

Patients were enrolled in this study between 1 December 1992 and 31 May 2009. After a follow-up period of 9.7 years (6.1, 14.0) [median (Q1, Q3)], 61 patients (13%) experienced a CV event, including cardiac death, myocardial infarction, repeat angiogram/angioplasty, stroke, coronary artery bypass graft surgery, and other vascular surgeries (carotid endarterectomy and peripheral vascular bypass; Tables 3 and 4).

Complications

Invasive coronary vasomotion testing was complicated by a procedure-related coronary dissection in three (0.6%) of 470 patients, all of which occurred before 2007. One of the dissections was mild and did not require stenting. The other two were managed with stenting, and the patients did well after the procedure. There were no deaths or myocardial infarctions associated with the procedure during the study period.

Framingham risk score

In univariate analysis, the FRS did not significantly predict the CV events [hazard ratio (HR) per 10% of predicted risk: 1.05, 95% CI 0.85–1.26, $P = 0.61$]. The estimated 10-year risk based on the FRS placed all 470

Table 1 Baseline patient characteristics by tertiles of Framingham risk score

Variables	Low	Intermediate	High	*P*
N (%)	277 (59)	117 (25)	76 (16)	
Age (mean ± SD) (years)	48 ± 11	57 ± 9	62 ± 8	< 0.001
Female [*N* (%)]	228 (82)	66 (56)	26 (34)	< 0.001
BMI (kg/m^2)	28 ± 6	29 ± 6	29 ± 6	0.27
Hypertension [*N* (%)]	80 (29)	58 (50)	49 (64)	< 0.001
Diabetes [*N* (%)]	10 (4)	11 (9)	19 (25)	< 0.001
Hypercholesterolemia [*N* (%)]	139 (50)	84 (72)	57 (75)	< 0.001
Family history CAD [*N* (%)]	167 (61)	82 (71)	48 (65)	< 0.2
Aspirin [*N* (%)]	121 (44)	62 (53)	40 (52)	0.15
ACE inhibitor [*N* (%)]	33 (12)	31 (27)	10 (13)	< 0.001
β-Blockers [*N* (%)]	81 (29)	34 (29)	21 (28)	0.96
Ca^{2+} channel blocker [*N* (%)]	80 (29)	48 (41)	28 (37)	0.04
Lipid lowering [*N* (%)]	102 (37)	55 (47)	29 (38)	0.16
Oral hypoglycemic [*N* (%)]	6 (2)	4 (3)	11 (14)	< 0.001
Insulin use [*N* (%)]	5 (2)	5 (4)	3 (4)	0.31
% ΔCBF	69 ± 193	47 ± 118	57 ± 98	0.48
% ΔCAD	− 14.8 ± 25	− 16.3 ± 25	− 15.2 ± 21	0.85
CFR	2.95 ± 0.7	2.7 ± 0.7	2.9 ± 0.6	< 0.001

Values are expressed as mean ± SD or *N* (%).
% ΔCAD, percent change in coronary artery diameter to acetylcholine; % ΔCBF, percent change in coronary blood flow to acetylcholine; CFR, coronary flow reserve.

Table 2 Baseline patient characteristics by microvascular endothelial function

Variables	Microvascular endothelial dysfunction	Normal microvascular endothelial function	*P*
N (%)	265 (56)	117 (25)	
Age (mean ± SD) (years)	54 ± 12	52 ± 12	0.03
Female [*N* (%)]	186 (70)	134 (65)	0.27
BMI (kg/m^2)	29 ± 6	28 ± 6	0.48
Hypertension [*N* (%)]	114 (43)	73 (46)	0.09
Diabetes [*N* (%)]	25 (9)	15 (7)	0.41
Hypercholesterolemia [*N* (%)]	157 (59)	123 (60)	< 0.85
Family history CAD [*N* (%)]	178 (69)	119 (60)	< 0.04
Aspirin [*N* (%)]	138 (52)	85 (41)	0.02
ACE inhibitor [*N* (%)]	42 (15)	32 (16)	0.94
β-Blockers [*N* (%)]	80 (30)	56 (27)	0.50
Ca^{2+}-channel blocker [*N* (%)]	94 (35)	62 (30)	0.25
Lipid lowering [*N* (%)]	118 (45)	68 (33)	0.01
Oral hypoglycemic [*N* (%)]	13 (5)	8 (4)	0.6
Insulin use [*N* (%)]	8 (3)	5 (2)	0.70
% ΔCBF	−10.9 ± 36	155 ± 212	< 0.001
% ΔCAD	−25.4 ± 21	−2.1 ± 23	< 0.001
CFR	2.78 ± 0.66	2.98 ± 0.7	< 0.001

Values are expressed as mean ± SD or *N* (%).
% ΔCAD, percent change in coronary artery diameter to acetylcholine; % ΔCBF, percent change in coronary blood flow to acetylcholine; CFR, coronary flow reserve.

Table 3 Distribution of cardiovascular events in the patient population by tertiles of Framingham risk score

Variable	Low	Intermediate	High	*P*
N = 61	277 (59)	117 (25)	76 (16)	
Cardiac death [*n* (%)]	1 (0.3)	2 (1.7)	2 (2.6)	0.01
Myocardial infarction [*n* (%)]	1 (0.3)	2 (1.7)	0	0.04
Repeat angiogram/PCI [*n* (%)]	18 (6.4)	14 (11.9)	6 (7.8)	0.11
Stroke [*n* (%)]	3 (1)	0	0	0.24
CABG [*n* (%)]	3 (1)	4 (3.4)	2 (2.6)	0.26
Other vascular surgery [*n* (%)]	1 (0.3)	2 (1.7)	0	0.16

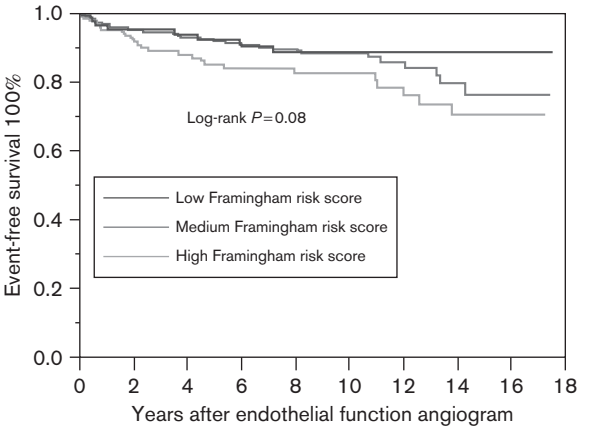
Values are expressed as *n* (%).
CABG, coronary artery bypass surgery; other vascular surgery includes endarterectomy and peripheral vascular bypass surgery.

patients in the intermediate risk category (10–20% risk) [3]. There was no difference in the incidence of CV events when patients were classified in the low (< 10%), intermediate (10–20%), and high (>20%) risk categories on the basis of the FRS Adult Treatment Panel III classification ($P = 0.08$ by Kaplan–Meier analysis; Fig. 1).

Microvascular coronary endothelial function

In univariate analysis microvascular CEF (% ΔCBF) was a significant predictor of CV events (HR per 50% increase in ΔCBF: 0.85, 95% CI 0.72–0.97, $P = 0.032$). The incidence of CV events was not different between patients with normal microvascular function and those with microvascular endothelial dysfunction (microvascular endothelial dysfunction was defined as ≤ 50% increase in CBF in response to the maximal dose of ACh compared with baseline CBF; $P = 0.36$ by Kaplan–Meier analysis; Fig. 2). After adjusting for the FRS, microvascular CEF was no longer a significant predictor of CV events (HR per 50% increase in ΔCBF: 0.88, 95% CI 0.74–1.01). When added to the FRS, microvascular CEF correctly reclassified 11.3% of the patients (NRI 0.11, 95% CI 0.019–0.21, $P = 0.02$). Eleven percent of the patients with events were incorrectly classified in a lower category and 21% of the patients with no events were correctly classified in a lower risk category, providing a net correct reclassification of 11.3% (Table 3).

Fig. 1



Kaplan–Meier curve showing the cumulative proportion of patients without cardiovascular events during follow-up. Status of the Framingham risk score is divided into low (< 10%), intermediate (10–20%), and high (>20%) risk on the basis of the ATPIII classification. ATPIII, Adult Treatment Panel III.

Epicardial coronary endothelial function

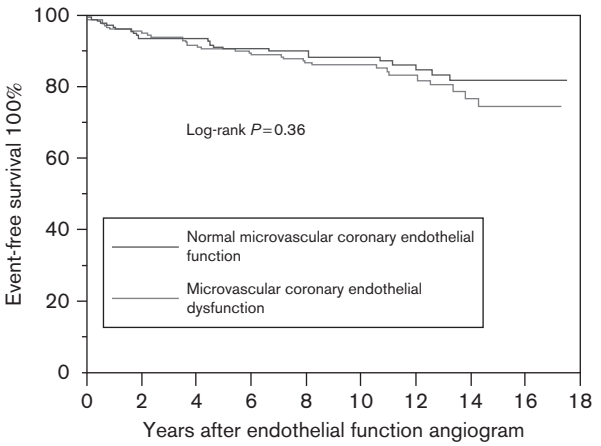
In univariate analysis, epicardial CEF (% ΔCAD) significantly predicted CV events (HR per 20% increase in ΔCAD: 0.73, 95% CI 0.59–0.90, $P = 0.01$). The incidence of CV events was significantly greater in patients with epicardial endothelial dysfunction than in those

Table 4 Distribution of cardiovascular events in the patient population by microvascular endothelial function

Variables	Microvascular endothelial dysfunction	Normal microvascular endothelial function	*P*
N (%)	265 (56)	117 (25)	
Cardiac death [*n* (%)]	3 (1.2)	2 (1.7)	0.01
Myocardial infarction [*n* (%)]	2 (0.8)	1 (0.8)	0.04
Repeat angiogram/PCI [*n* (%)]	25 (9.4)	13 (11.1)	0.11
Stroke [*n* (%)]	3 (1.2)	0	0.24
CABG [*n* (%)]	4 (1.5)	5 (4.3)	0.26
Other vascular surgery [*n* (%)]	1 (0.3)	2 (1.7)	0.16

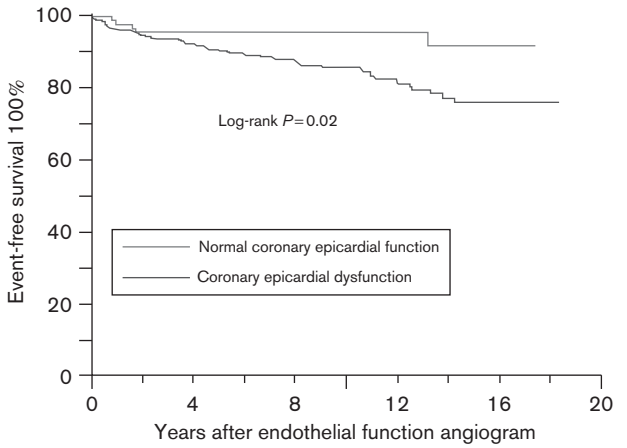
CABG, coronary artery bypass surgery; other vascular surgery includes endarterectomy and peripheral vascular bypass surgery.

Fig. 2



Kaplan–Meier curve showing the cumulative proportion of patients without cardiovascular events during follow-up. Status of microvascular coronary endothelial function is divided into normal microvascular endothelial function and microvascular endothelial dysfunction.

Fig. 3



Kaplan–Meier curve showing the cumulative proportion of patients without cardiovascular events during follow-up. Status of epicardial coronary endothelial function is divided into normal epicardial endothelial function and epicardial endothelial dysfunction.

vasodilated with ACh ($P=0.02$ by Kaplan–Meier analysis; Fig. 3). After adjusting for the FRS, epicardial CEF remained a significant predictor of CV events (HR per 20% increase in ΔCAD: 0.76, 95% CI 0.61–0.96). When added to the FRS, epicardial CEF correctly reclassified 12.1% of the patients (NRI 0.12, 95% CI −0.02 to 0.26, $P=0.09$), but it did not reach statistical significance. Five percent of patients with events were incorrectly classified in a lower category, and 23% of patients with no events were correctly classified in a lower risk category, yielding an NRI of 12.1% (Table 3).

When added to the FRS, the combined microvascular and epicardial CEF correctly reclassified 22.8% of the patients (NRI 0.23, 95% CI 8–36.7%, $P=0.001$). Only 3% of the patients with events were incorrectly classified in a lower category and 26% of patients with no events were correctly classified in a lower risk category, yielding a net correct reclassification of 22.8% (Tables 3 and 5).

Subanalysis in diabetics

To assess whether the FRS and CEF could predict the risk for CV events differently in patients with diabetes mellitus, we assessed separately for an interaction between diabetes and FRS, microvascular CEF, and epicardial CEF. No test for interaction yielded a significant result (*P*-value for FRS, 0.68; *P*-value for microvascular CEF, 0.56; and *P*-value for epicardial CEF, 0.79), suggesting that the risk for CV events predicted by the FRS, microvascular CEF, and epicardial CEF did not vary significantly between patients with and those without diabetes.

Discussion

The present study demonstrates that CEF testing is safe and adds significant value to the FRS, providing greater discrimination power for risk stratification of patients without obstructive coronary artery disease. The combination of microvascular and epicardial CEF provided the greatest value to FRS, with more than one in five individuals being correctly reclassified. Microvascular and epicardial endothelial function when used alone also provided modest value to the FRS with 12 and 11% of individuals, respectively, being reclassified correctly. The model incorporating epicardial CEF alone did not reach statistical significance. Thus, the current study further supports the clinical utility of individual assessment of endothelial dysfunction in risk stratification.

Traditional CV risk factors are not sufficient to correctly assign risk of development of CV disease in up to 50% of cases [23]. Indeed, the FRS, when applied to different populations, has shown inconsistent predictive value [24,25]. For example, the mortality data for the first 20 years in 12 cohorts of six countries showed that traditional risk factors are associated with risk only within certain cohorts [26]. Only age and mean blood pressure were universal predictors of coronary heart disease. In the current study, all patients were classified as intermediate risk when their 10-year absolute risk was calculated using the FRS alone. In univariate and multivariable models, the FRS was indeed not a significant predictor of CV events. Thus, there is a need for a more comprehensive method to assess risk in these individuals without CAD.

Several studies have tested different novel risk markers for improving CV risk assessment, especially in individual with intermediate risk [27,28], by providing greater

Table 5 Net reclassification improvement for CV events with addition of CEF to FRS ($N = 470$)

Variable	% Reclassified	Low (< 10%)	Intermediate (10–20%)	High (>20%)	% Net correct reclassification	NRI
FRS + microvascular CEF						
Events	11.5	7	54	0	0	0.11
Nonevents	21.5	87	321	1	21.2	
FRS + epicardial CEF						
Events	27.9	10	44	7	−4.9	0.12
Nonevents	30.3	110	285	14	23.5	
FRS + microvascular and epicardial CEF						
Events	26.2	9	45	7	−3.3	0.228
Nonevents	31.5	119	280	10	26.6	

CEF, coronary endothelial function; CV, cardiovascular; FRS, Framingham risk score; NRI, net reclassification improvement index.

discrimination of higher-risk and lower-risk patients within the intermediate-risk group [28]. AHA practice guidelines for assessment of CV risk in asymptomatic adults give recommendations on appropriate test modalities to further define risk in patients with intermediate risk [29]. In this study, we show that CEF testing in patients presenting with chest pain and found to have nonobstructive coronary artery disease on the diagnostic angiogram correctly reclassifies *22%* of the patients with intermediate risk on the basis of the FRS, with potential implications on risk management of these individuals.

Administration of intracoronary ACh is considered the reference standard in the assessment of epicardial and microvascular endothelial function [10]. Its use in clinical practice, however, still remains limited, possibly because of safety concerns related to its invasive nature. In the recent guidelines of the European Society of Cardiology on the management of stable coronary artery disease, the use of intracoronary ACh for assessment of CEF was endorsed and labeled as a class IIa indication [30], underscoring the need for better risk stratification in these patients. In the present study we demonstrate that comprehensive intracoronary physiology assessment to determine endothelial function is safe when performed by experienced operators. Our findings are consistent with those of a previous report demonstrating the safety of the assessment of endothelial function in women [31]. Additional barriers to adoption of this test are the lack of standardization of the testing protocol and difficulty in interpreting the results. Moreover, although several strategies aimed at reducing CV risk factors are associated with improvement in endothelial health, no single agent to date has been approved for the treatment of endothelial dysfunction *per se* [32]. Nevertheless, recent studies have shown that treatment of CV risk factors, which leads to improvement of peripheral endothelial function (vs. persistent endothelial dysfunction), is associated with an improved CV prognosis [33,34].

Several studies have shown an association between endothelial dysfunction (both in coronary and systemic circulation) as a marker of atherosclerotic risk and CV prognosis in patients with and those without coronary artery disease [5,7,8,35,36]. Endothelial dysfunction can be considered as a functional expression of inherent atherosclerotic risk, representing an integrated index of both the overall CV risk factor burden and the sum of all vasculoprotective factors in an individual. It may provide the link between CV risk factors and the progression of atherosclerotic disease [37].

Previous studies have shown that most atherosclerotic plaques responsible for future acute coronary syndromes occur in lesions associated with minimal luminal stenosis [38,39]. Lesion-related characteristics are thus crucial in determining vulnerable plaques in mild stenotic lesions and, by extension, in identifying patients at risk for cardiac events (vulnerable patients). We have previously shown that segments of the coronary epicardial arteries with endothelial dysfunction are associated with plaque characteristics typical of vulnerable plaques [40] and with the presence of a lipid core [14]. Moreover, segments with endothelial dysfunction are also those that ultimately progress to atherosclerotic plaques [14]. Thus, endothelial dysfunction may be an integral element in the evolution of a vulnerable plaque. Vulnerable plaques may be a potential mechanism by which coronary endothelial dysfunction causes an increase in CV events in vulnerable patients, and, thus, its detection may aid in more accurate risk stratification of patients classified as being at intermediate risk.

Study limitations

There are several limitations to our study. First, CV events were determined through questionnaires filled by the patients. A reviewer verified the events that occurred at our institution. We were, however, limited in verifying events that occurred elsewhere. Furthermore, the response rate for our questionnaires was 43%, which is comparable to that in other studies but is still a limitation of this study.

Second, we did not have intravascular ultrasound data on all patients to ascribe the site of endothelial dysfunction to the culprit coronary arteries. This would have provided a stronger link between segmental epicardial endothelial dysfunction and site of coronary CV events.

Third, our study was not designed to measure whether improvement in endothelial function with treatment

improves the prognosis of future CV events. Patients diagnosed with endothelial dysfunction may have been provided with treatment (at their physician's discretion), which might have improved endothelial function and led to regression to the mean of our results.

Fourth, there may have been a selection bias in the study, as the patients included in the study had a clinical indication for cardiac catheterization and may have potentially been different from the general population for whom the FRS was intended.

Conclusion

We demonstrated that, among patients presenting with chest pain or suspected ischemia, the assessment of CEF is safe, adds value to the FRS, and correctly reclassifies patients in the intermediate-risk category. This potentially has implications in risk management and treatment of these individual patients, and could be used in further risk stratification of patients, especially belonging to the intermediate-risk category with implications on risk reduction strategies.

Acknowledgements

This study was supported by grants from the NIH (K24 HL-69840, NIH R01 HL-63911, HL121561, DK100081, DK104273, HL123160, DK 73608), as well as by the Mayo Foundation.

Conflicts of interest

There are no conflicts of interest.

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